# Corticosteroid Pulse Therapy for the Treatment of Bullous Systemic Lupus Erythematosus with Lupus Nephritis

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Abstract: Systemic lupus erythematosus (SLE) is a multisystem autoimmune disease. Skin involvement occurs in nearly 76 % of all lupus patients. The Bullous Systemic Lupus Erythematosus (BSLE) is a rare cutaneous variant of SLE, affecting in less than 1%. A26-year-old female with a history of a vesiculobullous eruption on face, neck, trunks, andarms, along with oral mucosa ulcers.She hadphotosensitivity, a non-scarring alopecia, hemolytic anemia, serositis, arthralgia, renal impairment, and high antibody titers confirmingSLE. Histopathologicalexamination showed features in accordance with SLE, tends to beBSLE. The renal biopsy confirmed the features of lupus nephritis. The patient was diagnosed as BSLE based on the Systemic Lupus International Collaborating Clinics (SLICC) criteria, location of a blister, and histopathologicfinding. She responded well to systemic corticosteroid pulse therapy. BSLE should be considered as a differential diagnosis among patients with bullous lesions.It is vital to prevent the complication of SLE, that is lupus nephritis because it relates to a worse prognosis. We choose corticosteroid given as pulsed therapy to enhance the therapeutic effect and reduce the side effects, followed by azathioprine as sparing agent. Systemic corticosteroid pulse therapy is considered as first-line therapy, with azathioprine which has been proved to be effective in maintaining disease remission. The objectiveof BSLE therapy is to prevent new blisters, promote healing, and prevent scarring.Prognosis ad vitamdubiaadbonam, ad sanamdubiaadmalam, ad cosmetic dubiaadbonam.

## 1 INTRODUCTION

The systemic lupus erythematosus (SLE) is a multisystem autoimmune disease. The bullous systemic lupus erythematosus (BSLE) is a rare cutaneous variant of SLE, accounts less than 1%. BSLE is an autoantibody-mediated vesiculobullous disease in patients with SLE (Chen et al, 2015). The etiology of BSLE is unclear (Contestable et al, 2014). In the USA there is an association between SLE with HLA-DR2 (Wojnarowska et al, 2010; James et al, 2016). BSLE usually manifests in the second and third decades of life, most frequently in black women (Momen et al, 2016). If there is a bullous eruption, we have to consider BSLE as a differential diagnosis. Multiple case reports show that BSLE can be the initial presentation of SLE (Contestable et al, 2014; Momen et al, 2016). Here in we report a case of BSLE treated with corticosteroid pulse therapyas an alternative therapy to Dapsone.

## 2 CASE

A 26-year-old female was admitted to emergency department Dr. Kariadi General Hospital with a 1-week history of a progressive non-itching blistering eruption, erosion and crust around the face, neck, trunks, and arms. She also complained of diffuse hair loss, moderate fever, and arthralgias for the last three months. Bullae have appeared on the sun-exposed areas with the erythematous base while those on the arms had a clear base. There were histories of malar rash after sun exposure and conjunctivitis on the right eye. She has never had



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any seizure, psychosis, and history of blistering lesions before. She was not taking any drugs and never had a drug allergy. There is no family member with the same complaint. She weighed 42 kg with a height of 150 cm. Clinical examination revealed poor nutritional status with moderate pallor, bilateral pitting pedal edema with facial puffiness, and temperature (37.8°C). Her pulse rate was 92/min, Blood pressure was 110/70 mmHg, and respiration rate was 20/min. There was no enlargementon liver, spleen, and lymph node. The anogenital regions were spared. The dermatologicexamination demonstrated erosion and crusts on face, neck, trunks, and arms (Figure.1 A, B, C, D).Diffuse hair loss (Figure.1 E). Curdy white discharge was seen over the oral ulcers (Figure.1 F).

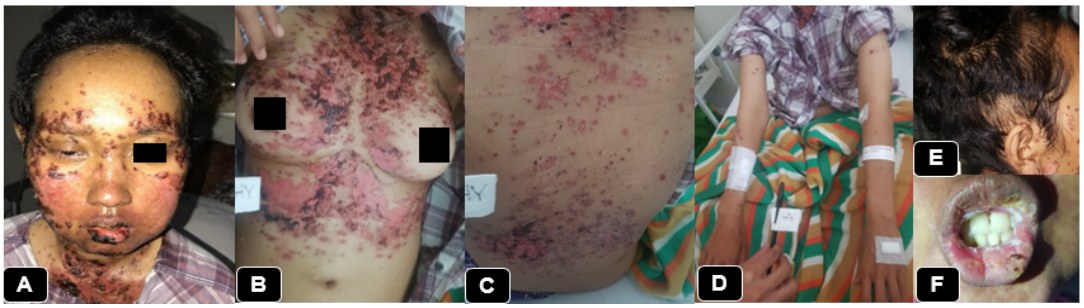


Figure 1. **A.** Erosion and crusts on the face, conjunctivitis on right eye **(B, C, D)** Erosion and crusts on the neck, trunks, and arms,**E.** Diffuse hair loss,**F.** Oral ulcers, and crust.

Based on the anamnesis and physical examination, there were several differential diagnoses: bullous systemic lupus erythematosus (BSLE) andpemphigus erythematosus with SLE (Senear-Usher syndrome). She was referred to the Department of Nephrology for kidney biopsy.Laboratory examination shows (Table.1).

Table.1. Laboratory examination

| EXAMINATION | RESULT |
|---|---|
| **Hematology** | - Haemoglobin 8,5 g/dL, increase RDW 16,4%<br>- Leukopenia 3,7x10$^3$/UL, lymphopenia 3% |
| **Blood Biochemistry** | - Increased serum creatinine 2,08 mg/dl and (Duplo test)<br>- Increased serum ureum 188 mg/dl (Duplo test).<br>- Creatinine clearance 30ml/min. Hypoalbuminemia (2,4 g/dl)<br>- Random Glucose Test (GDS), SGOT and SGPT within normal limits |
| **Peripheral blood smear** | - Anisocytosis, poikilocytosis (ovalosit, pearshape, teardrop, burr cell). |
| **Chest X-RAY** | - Cardiomegaly (LV, LA) |
| **ECG** | - Pericardial effusion with LvH concentric, no features of Myocarditis |
| **USG** | - Pleura effusion sinistra<br>- Bilateral cortical echogenicity increased, suggestive of renal parenchymal disease (Brenbridge 1). |
| **Urine Routine** | - Proteinuria 15mg/dl, Reduction 500mg/dl<br>- Leukocyte sediment 232,1/ul, leukocyte 25-30 LPB, glitter cell (+), cylinder 3,22/ul, hyaline cylinder 3,5 /ul<br>- Yeast cell 82,3/ul.Bacteria 7177,6/ul (++).<br>- Urinesbach 0 g/L volume 350 cc in 24 hour |
| **Immunology test** | - Serum *anti-nuclear antibodies* (ANA) 268,7 unit (> 60 positive)<br>- *Anti double-stranded DNA* (Anti dsDNA) 1098 IU/ml (> 300 Positive) |
| **Serologic test** | - Venereal Disease Research Laboratory (VDRL), HBsAg, and Human immunodeficiency virus (HIV) were negative. CD4: 137. |
| **Histopathology examination** | - Granulosis, spongiosis, and degeneration vacuolar(Figure 2A).<br>- Fibrous stromascattered with lymphocytes, histiocytes, perivascular in the papillary dermis(Figure 2B). |
| **Kidney biopsy** | - Diffuse Lupus Nephritis Class IV of ISN/RPS 2004 classification with an active lesion (Figure 2C). |

Based on anamnesis, physical examination, and laboratory examination, the patient was diagnosed as Bullous systemic lupus erythematosuswith lupus nephritis and oral thrush. The patient was managed with methylprednisolonepulse therapy 500mg/day (equivalent to prednisone 15 mg/kg/day) IV for three consecutive days, followed by half adjusting dose every three days until 32 mg/day orally (equivalent to prednisone 1 mg/kg/day) for one week. Azathioprine was started with 50 mg once daily peroral, ranitidine 150 mg twice a day IV, and systemic broad-spectrum antibiotics (ciprofloxacin) 500 mg twice a day, folic acid 1 mg once daily. The lesion was soaked with 0.9% NaCl for ± 15 minutes before the use of fusidic acid cream and silver sulfadiazine cream twice a day to erosions and crusts, nystatin drop 100,000 UI, 1cc / 8 hours for lesions in the oral cavity and triamcinolone acetonide in orabase. The results of the therapy are quite satisfactory. The patient is also given a whole blood transfusion to treat anemia. The patient was referred to Department of Nephrology for the treatment of lupus nephritis, and she was put on cyclophosphamide and lisinopril. She was discharged with no new skin lesions after 20 days.(Figure 2 D,E,F,G, H).

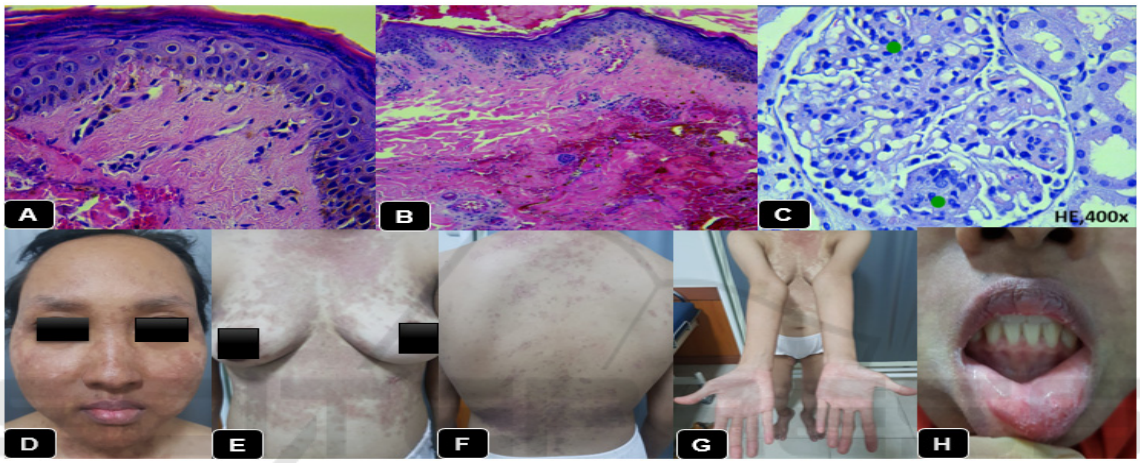


Figure 2. **A.**The epidermis**,** granulosis, spongiosis and degeneration vacuolar**B.** Dermis; subepidermalvesiculation, fibrous stromascattered with lymphocytes, histiocytes and perivascular inpapillary dermis**C.** Diffuse Lupus Nephritis Class IV**D, E, F, G.** Hyperpigmentedmacula on the face**,** neck, trunks, and arms **H.** No sign of oral ulcers

The patient was advised to visit a dermato-venereology clinic every two weeks to monitor side effects due to the long-term of topical and systemic corticosteroids, to do periodic blood, urine and serology tests, and to always use a sunscreen with SPF ≥30, 20 minutes before sun exposure.

## 3 DISCUSSION

The bullous systemic lupus erythematosus (BSLE) is a rare autoimmune blistering disorder that typically manifests as a vesiculobullous eruption in a patient with SLE.(Contestable et al, 2014) Clinically, BSLE is characterized by rapid onset of widespread, tense, clear or hemorrhagic fluid containing vesicles to bullae which rupture spontaneously resulting in erosions and crusts. These blisters are distributed over the neck, face, trunks, and extremities.The occurrence of blisters on the healthy skin should always arouse suspicion of BSLE. (Chen et al, 2015)

The diagnostic criteria of BSLE were first described by Camisa and Sharma in 1983 and were revised in 1988. These criteria were (1) diagnosis of SLE based on ACR criteria; (2) vesicles and/or bullae; (3) The histopathology is characterized by subepidermal bullae with microabscesses of neutrophils in the dermal papillae; (4) DIF with IgG and/or IgM and often IgA at the BMZ; and (5) IIF testing that can be negative or positive for circulating autoantibodies against the BMZ via the salt-split skin technique. (Contestable et al, 2014)

The American College of Rheumatology (ACR) revised criteria for SLE in 1997, which were recently validated by the Systemic Lupus International Collaborating Clinic (SLICC) group in 2012 that results in higher sensitivity with equal specificity (Table 2).(Kuhn et al, 2015)

Table 2. Classification of SLE based on the Systemic Lupus International Collaborating Clinic (SLICC) Criteria, and case

| Classification of SLE: The Systemic Lupus International Collaborating Clinic (SLICC) Criteria | Case |
|---|---|
| **Clinical criteria**<br>- The acute cutaneous lupus erythematosus (butterfly rash)<br>- The chronic cutaneous lupus erythematosus (discoid LE)<br>- Oral ulcers<br>- Non-scarring alope<br>cia<br>- Synovitis (≥ 2 joints) or tenderness on palpation (≥ 2 joints) and morning stiffness (≥ 30 minutes)<br>- Serositis (pleurisy / pericardial pain for > 1 day)<br>- Renal involvement (single urine: protein/ creatinine ratio/24-hour urine protein >0,5g)<br>- Neurological involvement (seizures, psychosis)<br>- Hemolytic anemia<br>- Leukopenia (<4000/μL) or lymphopenia (<1000/μL)<br>- Thrombocytopenia (<100.000/μL) | **Clinical criteria**<br>- Butterfly rash positive<br>- Negative<br>- Oral ulcers positive<br>- Positive, 3 months ago<br>- Arthralgia (ankle, interdigital)<br>- Pericardial and pleural effusion<br>- Proteinuria 15 mg/dl and Creatinine clearance 30 ml/min.<br>- Negative<br>- Anemia normositiknormokrom<br>- Leukopenia $3,7x10^3$/UL<br>- Within normal limits |
| **Immunological criteria**<br>- ANA level; above laboratory reference range<br>- Anti-dsDNA antibodies<br>- Anti-sm antibodies<br>- Antiphopolipid antibodies (anticardiolipin and anti-β2-glycoprotein I antibodies, false-positive VDRL test<br>- Low complement (C3, C4, or CH50)<br>- Direct coombs (in the absence of hemolytic anemia) | **Immunological criteria**<br>- ANA 268,7 unit (Positive > 60)<br>- Anti dsDNA 1098 IU/ml (Positive > 300)<br>- No examination<br>- VDRL negative<br>- No examination<br>- No examination |

(References: The Diagnosis and Treatment of Systemic Lupus Erythematosus)

According to the SLICC rule, the patient must manifest at least four criteria (including at least one clinical criterion and one immunologic criterion) or must have biopsy-proven lupus nephritis in the presence of either ANAs or anti-dsDNA antibodies (Contestable et al, 2014; Kuhn et al, 2015) Thehistopathological section in trunks erosion showed old lesion, and the feature view shows a central focus of degeneration vacuolar, subepidermalvesiculation, striking inflammatory changes outline the dermal vasculature. This is in accordance with the other features of BSLE(Calonje et al, 2012). Skin biopsy report only to corroborate our clinical impression and to form our final diagnosis. (Momen et al,2016)

Differential diagnosis of BSLE is pemphigus erythematosus with SLE (Senear-Usher syndrome). Senear-Usher syndrome can be ruled out because it is an autoimmune condition where there is overlap between the clinical and immunological features of pemphigus erythematosus and lupus erythematosus, include like scattered scaly flaccid blisters with erosions and crusts on 'seborrhoeic' areas along with malar rash, absence of mucous membrane involvement. ANA test is negative or weakly positive. Histopathological showedacanthotic epidermis with large subcorneal blisters.(Amatya et al,2017)

Dapsone is the initial treatment of choice for BSLE. (Contestable et al, 2014) The mechanism of actionmainly relies upon its inhibition of the functions of PMN leukocytes and of complement activation via the alternative pathway that has been postulated. (Chen et al, 2015) We didn't choose dapsone due to patient's hemolytic anemia and its unavailability in our facility. A corticosteroid may be active in patients who cannot tolerate dapsone, have an inadequate response to dapsone, or require treatment of concurrent systemic manifestations of systemic lupus erythematosus. (Visser et al, 2017)

Based on recommendations of GRh (German Society of Rheumatology) where corticosteroids as first-line therapy, begin with methylprednisolone 500–750 mg iv on three consecutive days (level of evidence 3, the strength of statement C); then per os 0.5 mg/kg body weight/day for four weeks with subsequent tapering.[6]Corticosteroid pulse therapy means it refers to treatment with more than 250 mg prednisone or its equivalent per day, for one or more days.The effects of corticosteroid pulse therapy appear to include downregulation of activation of immune cells and proinflammatory cytokine production, leading to reduced expression of

adhesion molecules and reduced movement of neutrophils into sites of inflammation. (Visser et al, 2017;Panat,2012) On this patient, we used methylprednisolone intermediate-acting with a low tendency to induce sodium and water retention. When decreasing corticosteroid doses, treatment with a sparing agent (azathioprine) regimen begins..(Visser et al, 2017) The aim of corticosteroid pulse therapy is getting quicker and stronger efficacy and decreasing the need for long-term use of steroids. (Panat,2012)

Azathioprinehas proved to be effective in maintaining disease remission. (Chen et al, 2015) It is a purine analog that inhibits the nucleic acid synthesis and affects both cellular and humoral immune functions. The drug is transformed to 6-mercaptopurine (6-MP) and then to its active metabolites, thiocyanic and thioguanine acid (6 TGN), which incorporate into DNA, thereby causing DNA/protein crosslinks and interfering with nucleic acid structure. The daily dose is 1 - 2.5 mg/kg. Regular monitoring of complete blood counts and liver function tests is required during therapy.(Visser et al, 2017)

Prognosis of this patient was ad vitamdubiaadbonam, ad sanamdubiaadmalam, ad cosmetic dubiaadbonam. The course of BSLE is often remitting. The disorder frequently resolves spontaneously in less than one year. BSLE is an autoimmune disease that tends to relapse. In some cases, post-inflammatory hypopigmentation may remain. The development of BSLE in patients with SLE does not typically lead to increased mortality. Morbidity depends on the extent of the eruption and the response to therapy.(Chen et al, 2015;Contestable et al, 2014; Kuhn et al, 2015).

## 4 CONCLUSION

BSLE should be considered as a differential diagnosis of patients with bullous lesions. Differentiation between BSLE and other blister disease is vital to prevent further complications of SLE that may coexist. Corticosteroid pulse therapy proved can be given as an alternative to Dapsone in BSLE with nephritis lupus.

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